Complete Summary

GUIDELINE TITLE

Parasitic infections. In: Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children.

BIBLIOGRAPHIC SOURCE(S)

Parasitic infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 74-90.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 16, 2008 - Antiepileptic drugs: The U.S. Food and Drug Administration (FDA) has completed its analysis of reports of suicidality (suicidal behavior or ideation [thoughts]) from placebo-controlled clinical trials of drugs used to treat epilepsy, psychiatric disorders, and other conditions. Based on the outcome of this review, FDA is requiring that all manufacturers of drugs in this class include a Warning in their labeling and develop a Medication Guide to be provided to patients prescribed these drugs to inform them of the risks of suicidal thoughts or actions. FDA expects that the increased risk of suicidality is shared by all antiepileptic drugs and anticipates that the class labeling change will be applied broadly.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Parasitic infections associated with human immunodeficiency virus (HIV) exposure or infection, including:

- Cryptosporidiosis/microsporidiosis
- Malaria
- Toxoplasmosis

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers

Nurses
Patients
Pharmacists
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide evidence-based guidelines for treatment and prophylaxis of opportunistic infections among HIV-exposed and HIV-infected children
- To serve as a companion to the United States Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) *Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Adults*

TARGET POPULATION

Human immunodeficiency virus (HIV)-exposed and HIV-infected infants, children, and adolescents living in the United States

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention/Counseling

1. Preventing exposure including counseling on avoidance of exposure and behavior modification
2. Preventing first episode of disease
    - Primary prophylaxis*
    - Discontinuing primary prophylaxis
3. Prevention of recurrence
    - Secondary prophylaxis*
    - Discontinuing secondary prophylaxis

Treatment/Management

1. Antiparasitic drug therapy*
2. Highly active antiretroviral therapy (HAART)
3. Monitoring and adverse events, including immune reconstitution inflammatory syndrome
4. Management of treatment failure

*__Note:__ Details of antiparasitic drug therapy and prophylaxis can be found in the "Major Recommendations" section of this summary and in Tables 1-6 of the original guideline document.

MAJOR OUTCOMES CONSIDERED

- Incidence of parasitic infections
- Treatment response
- Adverse drug reactions
- Clinically relevant drug interactions
- Immune reconstitution inflammatory syndrome

- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pediatric specialists with expertise in specific opportunistic infections were selected to review the literature since the last publication of the prevention and treatment guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Supporting the Recommendations

I: Evidence from at least one randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The current document combines recommendations for prevention and treatment of opportunistic infections (OIs) in human immunodeficiency virus (HIV)-exposed and -infected children into one document; it accompanies a similar document on prevention and treatment of OIs among HIV-infected adults prepared by a separate group of adult HIV and infectious disease specialists. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research (OAR) of the national Institutes for Health. Pediatric specialists with expertise in specific OIs were selected to review the literature since the last publication of the prevention and treatment guidelines, conferred over a period of several months, and produced draft guidelines.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating Scheme for Prevention and Treatment Recommendations

A: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered.**

B: Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. **Should generally be offered.**

C: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment or under consideration. **Optional.**

D: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered.**

E: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered.**

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations were reviewed and discussed by the Pediatric Opportunistic Infections (OI) Working Group at a meeting in Bethesda, Maryland, on June 25–26, 2007. The final document was prepared after this meeting, reflecting the discussion and further revisions at that meeting.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The quality of evidence supporting the recommendations (I-III) and the rating scheme for the recommendations (A-E) are defined at the end of the "Major Recommendations" field.

Refer to the original guideline document for information on epidemiology, clinical manifestations, and diagnosis of parasitic infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children.

Parasitic Infections: Cryptosporidiosis/Microsporidiosis

Prevention Recommendations

Preventing Exposure

Caregivers and HIV-infected children should be educated and counseled concerning the different ways that *Cryptosporidium* can be transmitted. Modes of transmission include direct contact with fecal material from adults, diaper-aged children, and infected animals; contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Hand-washing after exposure to potentially fecally contaminated material, including diapers, is important in reducing the risk of *Cryptosporidium*. HIV-infected children should not be allowed contact with ill pets or stool from pets, particularly dogs and cats <6 months of age; stray pets; or surfaces contaminated with human or animal stool. Direct contact with calves and lambs at farms or petting zoos should be avoided for HIV-infected children.

HIV-infected children should not be allowed to drink water directly from lakes or rivers, including swallowing water while swimming or playing in recreational water. Caregivers and HIV-infected children should be aware that lakes, rivers, salt-water beaches, certain swimming pools, recreational water parks, and ornamental water fountains might be contaminated with human or animal waste that contains *Cryptosporidium*.

Some outbreaks of cryptosporidiosis have been linked to consuming water from municipal water supplies. During outbreaks or in other situations in which a community advisory to boil water is issued, boiling water for ≥3 minutes will eliminate the risk for cryptosporidiosis and should be done for preparing infant formula as well as for drinking water.

Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., can be stored unrefrigerated on grocery shelves) are also safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe water source. Fruit juices that must be kept refrigerated from

the time they are processed to the time of consumption might be either fresh (i.e., unpasteurized) or heat treated (i.e., pasteurized); only those juices labeled as pasteurized should be considered free of risk from *Cryptosporidium*. Other pasteurized beverages also are considered safe to drink.

Cryptosporidium-infected patients should not work as food handlers, especially if the food to be handled is intended to be eaten without cooking.

In a hospital, standard precautions (i.e., use of gloves and hand-washing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person. However, because of the potential for fomite transmission, some experts recommend that severely immunocompromised HIV-infected patients should not share a room with a patient with cryptosporidiosis **(CIII)**.

Similar to precautions for prevention of cryptosporidiosis, general attention to hand-washing and other personal hygiene measures will reduce exposure to microsporidia as well.

Preventing First Episode of Disease

Because chronic *Cryptosporidium* infection occurs most frequently in HIV-infected individuals with advanced immune deficiency, antiretroviral treatment of HIV-infected children prior to the development of severe immune deficiency is a primary modality of prevention.

Some observational studies from the pre-highly active antiretroviral therapy (HAART) era suggested that rifabutin or clarithromycin prophylaxis for *Mycobacterium avium* complex (MAC) may be associated with decreased rates of cryptosporidiosis. However, the data are conflicting and insufficient to recommend using these drugs solely for prophylaxis of cryptosporidiosis. No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treatment of Disease

Immune reconstitution resulting from HAART will frequently result in clearance of *Cryptosporidium* and *Microsporidium* infections. Effective HAART is the primary initial treatment for these infections in HIV-infected children and adults **(AII)**. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided **(AIII)**. Antimotility agents should be used with caution among young children **(CIII)**.

<u>Cryptosporidium</u>

No consistently effective therapy is available for cryptosporidiosis and duration of treatment among HIV-infected persons is uncertain. Multiple agents have been investigated in small randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *C. parvum* has yet been shown consistently effective and durable when used alone without concomitant antiretroviral therapy.

A review of clinical trials of treatment of *Cryptosporidia* in immunocompromised patients, including those with HIV infection, by the Cochrane Collaboration found that no agent has proven efficacy for the treatment of cryptosporidiosis among immunocompromised patients; however, in immunocompetent individuals, nitazoxanide reduces the load of parasites. Given the seriousness of this infection among immunocompromised individuals, use of nitazoxanide can be considered in immunocompromised HIV-infected children in conjunction with HAART for immune restoration **(CIII)**.

Nitazoxanide is approved in the United States for treatment of diarrhea caused by *Cryptosporidium* and *Giardia lamblia* among children and is available in a liquid and tablet formulation (**BI** for HIV-uninfected and **CIII** for HIV-infected children). An Egyptian clinical trial among 100 HIV-uninfected adults and children randomized patients to a 3-day course of nitazoxanide or placebo. Nitazoxanide therapy reduced the duration of both diarrhea and oocyst shedding; among children, clinical response was 88% with nitazoxanide and 38% with placebo. No substantial adverse events were reported, and adverse events that were reported were similar in the treatment and placebo groups in this study. A study in Zambia among 100 malnourished children aged 12–35 months (half HIV infected) reported a clinical response of 56% with treatment compared to 23% with placebo among HIV-uninfected children, but among HIV-infected children with low CD4 counts, the drug was no more effective than placebo. These results may be due to the short course (3 days) of therapy as retreatment for additional 3 days increased the number of responders. In a study among HIV-infected adults who had CD4 counts >50 cells/mm^3, 14 days of nitazoxanide resulted in 71% (10 of 14) response using 500 mg twice daily and 90% (9 of 10) using 1,000 mg twice daily, compared with 25% with placebo. The recommended dose for children is 100 mg orally twice daily for children aged 1 to 3 years and 200 mg twice daily for children aged 4 to 11 years. A tablet preparation (500 mg twice daily) is available for children aged ≥12 years. All medications should be given with food.

Paromomycin is a nonabsorbable aminoglycoside indicated for the treatment of intestinal amebiasis that is effective for treatment of cryptosporidiosis in animal models but is not specifically approved for cryptosporidiosis. A Cochrane Review and a meta-analysis of the two randomized controlled trials comparing paromomycin with placebo among adults with AIDS found the drug was no more effective than placebo at reducing diarrheal frequency or parasite burden, and a clinical response to paromomycin is rare in patients with CD4 count <100 cells/mm^3. Therefore, data do not support a recommendation for the use of paromomycin for cryptosporidiosis **(DII)**.

Azithromycin has demonstrated some activity against *C. parvum* infection in a limited number of HIV-infected children. An azithromycin regimen of 10

mg/kg/day on Day 1, and 5 mg/kg/day on Days 2 to 10 was successful in rapidly resolving enteric symptoms in three of four HIV-infected children with cryptosporidiosis. However, data are insufficient to recommend use of this drug to treat cryptosporidial infection **(CIII)**.

Microsporidium

Albendazole has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *Vittaforma corneae*. Albendazole decreased diarrhea, sometimes with eradication of the organism in some studies]. Albendazole is recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII)**.

No specific therapeutic agent is available for *Enterocytozoon bieneusi* infection. Fumagillin ® (Sanofi-Synthelabo Laboratories, Gentilly, France), a water-insoluble antibiotic made by *Aspergillus fumigatus*, or its synthetic analog TNP-470 have been shown to have anti-microsporidial activity and have been used to treat microsporidiosis in animals and humans. In a placebo-controlled study of immunocompromised adults (including HIV-infected adults) with *Enterocytozoon bieneusi* microsporidiosis, fumagillin (20 mg/dose orally three times daily for 2 weeks) was associated with decreased diarrhea and clearance of microsporidial spores, which was not observed in placebo patients. No data are available on use of fumagillin or TNP-470 among HIV-infected children, and neither drug is available in the United States. Data are insufficient to make recommendations on use of these drugs in children **(CIII)**. One report indicated that treatment with nitazoxanide for 60 days might resolve chronic diarrhea caused by *Enterocytozoon bieneusi* in the absence of antiretroviral therapy, but this effect was minimal among patients with low CD4 counts, and therefore may be of limited utility **(CIII)**.

Keratoconjunctivitis caused by microsporidia among HIV-infected adults responds to topical therapy with investigational fumagillin eye drops prepared from Fumidil-B® (fumagillin bicyclohexylammonium, a commercial product used to control a microsporidial disease of honeybees) in saline (to achieve a concentration of 70 micrograms/mL of fumagillin) **(BII)**. The combination of albendazole and fumagillin has demonstrated consistent activity against microsporidia *in vitro* and is recommended for ocular infections, in addition to topical therapy, as microsporidia may remain present systemically despite clearance from the eye with topical therapy alone **(BIII)**.

Metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis **(DII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In patients who are severely ill, total parenteral nutrition may be indicated **(CIII)**.

Nitazoxanide has not been associated with substantial side effects. Albendazole side effects are rare but hypersensitivity (e.g., rash, pruritis, fever), neutropenia (reversible), central nervous system (CNS) effects (e.g., dizziness, headache), gastrointestinal (GI) disturbances (e.g., abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Dose-related bone marrow toxicity is the principal adverse effect of fumagillin, with reversible thrombocytopenia and neutropenia being the most frequent adverse events; topical fumagillin has not been associated with substantial side effects.

IRIS has not been described in association with treatment of cryptosporidiosis or with treatment for *E. bieneusi* or non-*E. bieneusi* microsporidiosis.

Management of Treatment Failure

The only feasible approaches to management of treatment failure are supportive treatment and optimizing antiretroviral therapy to achieve full virologic suppression **(AIII)**.

Prevention of Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis or microsporidiosis. However, treatment for ocular microsporidiosis should be continued indefinitely because recurrence or relapse might follow treatment discontinuation **(BIII)**.

Discontinuing Secondary Prophylaxis

Not applicable.

Parasitic Infections: Malaria

Prevention Recommendations

Preventing Exposure

HIV-infected children, particularly those with immunosuppression, should be advised to use personal protective measures to prevent mosquito bites if traveling to endemic areas. Specifically, clothing can be impregnated with permethrin, effective for weeks even through 10 washings **(AI)**. Long-acting N,N-diethyl-meta-toluamide (DEET) mosquito repellents (30%−50% concentration) are very practical and 99% effective when combined with permethrin-treated clothing **(AI)**. DEET should be applied onto young children by caregivers and generally should not be applied to young children's hands **(AIII)**. Specific instructions by providers on product purchasing and use are invaluable. Insecticide treated bed nets are inexpensive and readily available in endemic countries. All children, regardless of their HIV-status, should sleep under an insecticide treated bed net when traveling in malaria-endemic areas.

Primary Prophylaxis

U.S.-born children of immigrant parents traveling to endemic regions are at especially high risk of acquiring malaria. Child immigrants or second-generation immigrant children whose caregivers are from malaria-endemic areas are likely to travel to high-risk destinations and be more susceptible than their caregivers due to lack of previous malaria exposure **(AII)**. These children and their caregivers are at especially high risk of acquiring malaria. Children who will be traveling to malaria-endemic regions should receive pretravel counseling on insect avoidance techniques and receive appropriate chemoprophylaxis. Recommendations for chemoprophylaxis are the same for HIV-infected persons as for noninfected persons and are available at the Centers for Disease Control and Prevention (CDC) Web site (http://www.cdc.gov/malaria/).

There is the potential for antiretroviral and antimalarial drug-drug interactions. Specifically, mefloquine significantly decreases steady-state ritonavir area under the curve plasma levels by 31%. In children receiving a boosted protease inhibitor (PI) regimen with pre-existing moderate resistance, this decrease may indeed be significant. In addition, antimalarial medications may need special preparation and some are not easily delivered to children. Therefore, it is advisable that patients planning to travel to malaria-endemic areas visit a travel medicine specialist with training and experience in pediatrics ≥2 weeks prior to departure **(AII)**.

In nonholoendemic areas, there is some protection with trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis in combination with the use of bed nets, resulting in >90% reduction in clinical malaria in one study. However, TMP-SMX is not recommended as an antimalarial prophylactic regimen by the CDC, and HIV-infected travelers must not rely on TMP-SMX for chemoprophylaxis against malaria.

Discontinuing Primary Prophylaxis

Travel-related chemoprophylaxis with chloroquine, mefloquine, and doxycycline is generally discontinued 4 weeks after leaving a malaria-endemic area since these drugs are not effective against the developing malaria in the liver and only kill the malaria once it has emerged to infect the red blood cells. Atovaquone-proguanil is discontinued 1 week after leaving malaria-endemic areas. Chemoprophylaxis is not 100% effective, and malaria should be included in the differential diagnosis of anyone having traveled in the previous 12 months to a malaria-endemic area who presents with fever or other signs or symptoms consistent with malaria.

Treatment Recommendations

Treatment of Disease

Treatment of malaria is based on the severity of disease, age of onset, malaria species, and known resistance patterns **(AI)**. It is unclear whether there is a difference in response to antimalarial treatment in relation to HIV infection status. HIV-infected or -exposed children are frequently excluded from drug efficacy trials because of cotrimoxazole prophylaxis. Current published studies have conflicting results, have used older antimalarials, or were not adequately powered to answer this question. HIV infection status should not affect choice of therapy and there are currently no recommendations for alternative dosing of antimalarial drugs in HIV-infected individuals **(AII)**. A full discussion of treatment in children is beyond

the scope of this document but has been addressed elsewhere. Treatment dosing for adolescents and children is provided in Table 4 in the original guideline document. In addition, up-to-date malaria treatment recommendations are available from the CDC at http://www.cdc.gov/malaria/pdf/treatmenttable.pdf

Plasmodium falciparum

Uncomplicated chloroquine-sensitive *Plasmodium (P.) falciparum* malaria should be treated with chloroquine. The recommended treatment options for uncomplicated chloroquine-resistant *P. falciparum* in the United States are: atovaquone-proguanil (Malarone™), quinine with clindamycin or doxycycline (in children aged ≥8 years), or mefloquine (Lariam™) **(AI)**. For dosages, refer to the CDC Web site mentioned above. It is imperative that the clinician choose a medication according to known sensitivity patterns from the area where the malaria was acquired.

The current drug of choice for uncomplicated chloroquine-resistant *P. falciparum* malaria is atovaquone-proguanil, which is Food and Drug Administration (FDA) approved for use in children weighing >5 kg, is well tolerated, has a wide therapeutic window, and provides simple dosing with pediatric tablets available. Although mefloquine is FDA approved for ages >6 months, pediatric tablets are not available. However, mefloquine is the only treatment choice for uncomplicated chloroquine-resistant *P. falciparum* malaria in children weighing <5 kg.

Severe *P. falciparum* should be treated with intravenous quinidine gluconate (or intravenous quinine when available). Duration of quinine/quinidine therapy is typically 3 days with clindamycin, or doxycycline, continued for 7 days **(AI)**. Intravenous quinidine can cause hypoglycemia, ventricular arrhythmia, and QT prolongation; therefore close monitoring, including telemetry, is required during infusion. Increasingly, quinidine is not always stocked by hospital pharmacies. Ritonavir inhibits quinidine metabolism and is considered a contraindication. An alternative is artesunate, which is available from the CDC on an investigational new drug (IND) protocol. When there are signs or symptoms of severe disease, especially when there are indicators of a poor prognosis (including clinical features of impaired level of consciousness, respiratory distress, jaundice, seizures, or shock or laboratory features of hypoglycemia, elevated bilirubin, acidosis, elevated liver aminotransferase levels, or renal insufficiency), a tropical medicine specialist should be consulted. For artesunate release or additional assistance, contact the 24-hour CDC malaria hotline at 770-488-7788 during the day and 770-488-7100 after hours, weekends, and holidays.

P. vivax, P. ovale, P. malariae

The medication of choice for non-*P. falciparum* malaria is chloroquine; the organisms are generally sensitive to this drug **(AI)**. Chloroquine is generally well tolerated. The most common reaction is self-limited itching (2%), especially in persons of African descent (50%); this is not an allergy and should not be considered a contraindication to treatment with chloroquine. However, there are exceptions where *P. vivax* has known high rates of chloroquine resistance, most notably in New Guinea. A patient infected with known or suspected chloroquine-resistant *P. vivax* malaria should receive an alternative first-line agent (i.e., quinine plus clindamycin or doxycycline, atovaquone-proguanil, mefloquine). Both

P. vivax and *P. ovale* have an intrahepatic stage (hypnozoite) that is not treated with the acute blood stage medications mentioned. In order to prevent relapse of *P. vivax* or *P. ovale* infection, patients should receive presumptive antirelapse therapy with primaquine following the primary blood stage treatment **(AI)**. Glucose-6-phosphate dehydrogenase deficiency **must** be excluded prior to any primaquine use due to the risk of severe hemolytic anemia.

Unknown Species Type

When reliable identification of the malaria species is not possible or in a severely ill individual, clinicians should always treat for the worst case scenario of chloroquine-resistant *P. falciparum* malaria **(AIII)**. Polymerase chain reaction assays are now commercially available and can be used to speciate when microscopy is not sufficient. Assistance with speciation is also available from state public health departments and the CDC's Division of Parasitic Diseases diagnostic service (http://www.dpd.cdc.gov/). After completion of initial therapy, knowing the malaria species is important since presumptive antirelapse therapy is necessary for *P. ovale* and *P. vivax*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Severe malaria commonly induces hypoglycemia in children, especially when treated with intravenous quinine/quinidine due to the inhibition of gluconeogenesis and induction of endogenous insulin production. Therefore, it is prudent to use a crystalloid solution containing glucose for fluid maintenance while closely monitoring glucose levels until intravenous quinine/quinidine therapy has been completed. Monitoring glucose is especially important for infants and individuals with altered mental status. Cardiac and intensive care monitoring is recommended as quinine/quinidine can cause hypotension and may widen the QRS interval. Another common adverse reaction (50%−75%) to quinine is tinnitus, although this generally resolves following treatment.

Management of Treatment Failure

Treatment failure with *P. falciparum* among children receiving a full course of appropriate antimalarial therapy is uncommon but may occur. Patients should be monitored for clinical response as well as for signs of recrudescence after therapy completion. Current published studies do not have the power to detect a difference in treatment outcomes in HIV-infected compared to HIV-uninfected children. Relapse of *P. vivax* and *P. ovale* can occur from the dormant (hypnozoite) liver form but is less common if primaquine treatment is given. Malaria medications purchased in sub-Saharan Africa or Southeast Asia may be counterfeit.

Prevention of Recurrence

With the exception of reactivation of *P. vivax* and *P. ovale* hypnozoites, malaria, once successfully treated, does not recur. Malaria infection does not infer protective immunity and continued exposure to malaria parasites can result in repeated infection.

Discontinuing Secondary Prophylaxis

Not applicable.

Parasitic Infections: Toxoplasmosis

Prevention Recommendations

Preventing Exposure

All HIV-infected children, adolescents, and their caregivers should be counseled regarding sources of *Toxoplasma gondii* infection. They should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison **(BIII)**. Specifically, lamb, beef, and pork should be cooked to an internal temperature of 165 degrees F–170 degrees F; meat cooked until it is no longer pink inside usually has an internal temperature of 165 degrees F–170 degrees F and therefore, from a more practical perspective, satisfies this requirement. Hands should be washed after contact with raw meat and after gardening or other contact with soil; in addition, fruits and vegetables should be washed well before eating them raw **(BIII)**. Stray cats should not be handled or adopted; if there is a cat in the household, it is advised to keep the cat inside and the litter box should be changed daily, preferably by an HIV-negative, nonpregnant person **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis **(EII)**.

Preventing First Episode of Disease

Toxoplasma-seropositive adolescent and adult patients who have a CD4 count of <100 cells/ mm^3 should be administered prophylaxis against Toxoplasma encephalitis (TE) **(AII)**. Specific levels of immunosuppression that increase the risk of developing TE in children are less well defined. *Toxoplasma*-seropositive children with CD4 <15% should be administered prophylaxis against TE **(BIII)**. For children aged >6 years, the same absolute CD4 cell count level as for HIV-infected adults can be used **(BIII)**.

In HIV-infected adolescents and adults, the double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is effective against TE as well and is therefore recommended **(AII)**. TMP-SMX, one double-strength tablet three times weekly (or 3 consecutive days a week), is an alternative **(BIII)**. There are limited data on the efficacy of TMP-SMX as a primary preventive agent for TE in children. However, based upon adult data, it is also the regimen of choice in children **(BIII)**; for pediatric dosage recommendations see Table 1 in the original guideline document. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which is also effective against PCP **(BI)**. Atovaquone with or without pyrimethamine also can be considered **(CIII)**. Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data **(DII)**. Aerosolized pentamidine does not protect against TE and is not recommended **(EI)**. *Toxoplasma*-seronegative adults and adolescents who are not taking a PCP-prophylactic regimen known to be active against TE should be retested for IgG

antibody to *Toxoplasma* when their CD4 count declines to <100 cells/mm^3 to determine whether they have seroconverted and are therefore at risk for TE **(CIII)**. Severely immunosuppressed children who are not receiving TMP-SMX or atovaquone who are determined to be seropositive for *Toxoplasma* should be administered prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine) **(BIII)**.

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued among HIV-infected adult and adolescent patients who have responded to HAART with an increase in CD4 count to >200 cells/mm^3 for >3 months **(AI)**. Multiple observational studies and two randomized trials have reported that primary prophylaxis can be discontinued with minimal risk for experiencing TE recrudescence among patients who have responded to HAART with an increase in CD4 count from <200 cells/ mm^3 to ≥200 cells/ mm^3 for >3 months. Although patients with CD4 counts of <100 cells/mm^3 are at greatest risk for experiencing TE, the risk for TE occurring when CD4 count has increased to 100 – 200 cells/mm^3 has not been studied as rigorously as an increase to >200 cells/mm^3. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/mm^3. Discontinuing primary TE prophylaxis is recommended because prophylaxis adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. There are no data on the safety of discontinuing primary TE prophylaxis for HIV-infected children whose CD4 percentage rises above 15%. Based upon adult data, it may be safe to discontinue TMP-SMX once a child responds to HAART with a sustained rise in their CD4 percentage above 15%; for children aged >6 years, the same CD4 count as for HIV-infected adults can be used **(CIII)**.

Prophylaxis should be reintroduced in HIV-infected adults and adolescents if CD4 count decreases to <100–200 cells/mm^3 **(AIII)** or CD4 percentage falls below 15% for HIV-infected children **(BIII)**.

Treatment Recommendations

Treatment of Disease

Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate specialist. Although controversy exists regarding the efficacy of treatment of pregnant women with acute toxoplasmosis in an attempt to prevent infection of the fetus, most experts would recommend such therapy. If an HIV-infected woman has a symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered whether or not the mother was treated during pregnancy **(BIII)**. Absent definitive data, some experts would recommend treating HIV-infected infants longer than uninfected infants.

The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII)**. Although the optimal

duration of therapy is undefined, the recommended duration of treatment of congenital toxoplasmosis for infants without HIV infection is 12 months **(AII)**. Absent definitive data, the same recommendation applies to HIV-infected children with congenital toxoplasmosis.

For children without HIV infection who have mild congenital toxoplasmosis, certain experts alternate pyrimethamine/sulfadiazine/folinic acid monthly with spiramycin from months 7 to 12 of treatment **(CIII)**. However, among children with moderate-to-severe disease and those with HIV infection, the full 12-month regimen of pyrimethamine/sulfadiazine should be administered **(AII)**.

HIV-infected children with acquired CNS or ocular or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(AI)**. Acute therapy should be continued for 6 weeks, assuming clinical and radiological improvement **(BII)**. Longer courses of treatment might be required in cases of extensive disease or poor response after 6 weeks. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin **(AI)**. Azithromycin also has been used with pyrimethamine and leucovorin among sulfa-allergic adults instead of clindamycin, but this regimen has not been studied among children **(CIII)**.

Other alternatives in adults are atovaquone plus pyrimethamine and leucovorin, or atovaquone with sulfadiazine alone, or atovaquone as a single agent among patients intolerant to both pyrimethamine and sulfadiazine **(BII)**; however, these regimens have not been studied among children **(CIII)**. TMP-SMX alone has been used as an alternative to pyrimethamine-sulfadiazine among adults, but this has not been studied among children **(CIII)**.

For isolated ocular toxoplasmosis in non-immunocompromised hosts, TMP-SMX alone has been shown to be as effective as pyrimethamine-sulfadiazine. However, these data have not been duplicated in HIV-infected persons and therefore this regimen cannot be recommended for this group of patients.

Corticosteroids (e.g., dexamethasone or prednisone) are recommended for children with CNS disease when cerebrospinal fluid (CSF) protein is very elevated (i.e., >1,000 mg/dL) or with focal lesions with substantial mass effects **(BIII)**. Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible.

Anticonvulsants should be administered to children with TE who have a history of seizures **(AIII)**, but should not be administered prophylactically to all patients **(DIII)**. Anticonvulsants, if administered, should be continued at least through the period of acute therapy.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

Children with TE should be routinely monitored for clinical and radiologic improvement and for adverse effects of treatment; changes in antibody titers are not useful for monitoring responses to therapy.

IRIS has been described only rarely in HIV-infected adults and has not been described in pediatric HIV-infected patients.

Pyrimethamine can be associated with rash (including Stevens-Johnson syndrome) and nausea. The primary toxicity of pyrimethamine is reversible bone marrow suppression (i.e., neutropenia, anemia, and thrombocytopenia). A complete blood count should be performed at least weekly while the child is on daily pyrimethamine and at least monthly while on less than daily dosing **(AIII)**. Leucovorin (folinic acid) always should be administered with pyrimethamine; increased doses of leucovorin might be required in the event of marrow suppression. Because of the long half-life of pyrimethamine, leucovorin should be continued 1 week after pyrimethamine has been discontinued.

Adverse effects of sulfadiazine include rash, fever, leukopenia, hepatitis, GI symptoms (e.g., nausea, vomiting, and diarrhea), and crystalluria. Clindamycin can be associated with fever, rash, and GI symptoms (e.g., nausea, vomiting, and diarrhea, including pseudomembranous colitis) and hepatotoxicity.

Drug interactions between anticonvulsants and antiretrovirals should be evaluated. Patients receiving corticosteroids should be closely monitored for development of other opportunistic infections (OIs).

Management of Treatment Failure

Brain biopsy should be considered when there is early clinical or radiologic neurologic deterioration despite adequate empiric treatment or among children who fail to clinically respond to anti-*Toxoplasma* therapy after 10 to 14 days. For children who undergo brain biopsy and have confirmed histopathologic evidence of TE despite treatment, a switch to an alternative regimen as previously described should be considered **(BIII)**.

Prevention of Recurrence

Patients who have completed initial therapy for acquired TE should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI)** unless there is immune reconstitution with antiretroviral therapy. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective for this purpose **(AI)**. A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin **(BI)**; however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well **(AII)**. Based on adult data, atovaquone with or without pyrimethamine also can be considered for children **(CIII)**. Limited data support the use of TMP-SMX for secondary prophylaxis; this regimen should only be used for persons not tolerant to pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CII)**.

Discontinuing Secondary Prophylaxis

Adult and adolescent patients receiving secondary prophylaxis for acquired TE are at low risk for recurrence of TE when they have successfully completed their initial therapy, remain asymptomatic with regard to signs and symptoms of TE, and

have a sustained increase in their CD4 count of >200 cells/mm^3 after HAART (e.g., >6 months). Discontinuing chronic maintenance therapy in HIV-infected adolescents and adults who meet these criteria is a reasonable consideration **(BI)**. It appears that the highest risk for relapse occurs within the first 6 months of stopping secondary prophylaxis. Certain specialists would obtain an MRI (magnetic resonance imaging) of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate. The safety of discontinuation of secondary prophylaxis after immune reconstitution with HAART among children has not been studied extensively. However, given the data in adults, clinicians caring for HIV-infected children aged <6 years can consider discontinuing secondary prophylaxis against *Toxoplasma gondii* after they have completed TE therapy and are asymptomatic and once the CD4 percentage has risen above 15% for ≥6 months on stable HAART; for children aged >6 years, the same CD4 count used in adults (CD4 >200 cells/ mm^3) can also be used **(BIII)**. Prophylaxis should be reinstituted if these parameters are not met.

Definitions:

Rating Scheme for Prevention and Treatment Recommendations	
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered.**
B	Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. **Should generally be offered.**
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. **Optional.**
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered.**
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered.**
Quality of Evidence Supporting the Recommendation	
I	Evidence from at least one randomized, controlled trial.

II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate prevention and treatment of parasitic infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children

POTENTIAL HARMS

Adverse Drug Effects and Drug Interactions

Major toxicities and interactions of the drug preparations used in treatment of opportunistic infections are discussed in the "Major Recommendations" section of this summary and in Table 5 in the original guideline document. Drug interactions of clinical significance are discussed in Table 6 in the original guideline document.

CONTRAINDICATIONS

CONTRAINDICATIONS

A list of drug contraindications for prevention of drug interactions is provided in Table 6 of the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Treatment of opportunistic infections is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Parasitic infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 74-90.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Centers for Disease Control and Prevention (CDC), their planners, and their content specialists wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. This report does not include any discussion of the unlabeled use of a product or a product under investigational use.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 20, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was most recently updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium). This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs. This NGC summary was updated by ECRI Institute on August 24, 2009.

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